Complete Summary

GUIDELINE TITLE

Preoperative or postoperative therapy for resectable esophageal cancer: guideline recommendations.

BIBLIOGRAPHIC SOURCE(S)

Malthaner RA, Wong RK, Spithoff K, Rumble RB, Zuraw L, Gastrointestinal Cancer Disease Site Group. Preoperative or postoperative therapy for resectable esophageal cancer: guideline recommendations. Toronto (ON): Cancer Care Ontario (CCO); 2008 May 21. 57 p. (Evidence-based series; no. 2-11). [86 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Resectable esophageal cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Treatment

CLINICAL SPECIALTY

Gastroenterology
Internal Medicine
Oncology
Radiation Oncology
Surgery

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate whether patients with resectable esophageal cancer should receive preoperative or postoperative therapy along with surgery

TARGET POPULATION

Adult patients with respectable, operable, and potentially curable thoracic (lower two thirds of esophagus) esophageal cancer for whom surgery is considered appropriate

INTERVENTIONS AND PRACTICES CONSIDERED

1. Preoperative therapy that includes the following, in combination or alone:
    - Chemotherapy (CT)
    - Radiotherapy (RT)
    - Hyperthermia with chemoradiotherapy (CRT)

2. Postoperative therapy that includes the following, in combination or alone:
    - CT
    - RT
    - Immunotherapy with RT or CRT

MAJOR OUTCOMES CONSIDERED

- Median survival time
- Five-year survival rate
- Progression-free survival
- Overall survival
- Duration of improved dysphagia
- Adverse effects of chemotherapy and radiotherapy
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

MEDLINE (1966 to April week 3, 2007), EMBASE (to week 17, 2007), CANCERLIT (1983 to October 2001) and the Cochrane Library (2007, Issue 2) databases were searched with no language restrictions. "Esophageal neoplasms" (Medical subject heading (MeSH)) was combined with "chemotherapy, adjuvant" (MeSH), "radiotherapy, adjuvant" (MeSH), "immunotherapy, adjuvant" (MeSH), and each of the following phrases used as text words: "preoperative", "neoadjuvant", "chemotherapy", "radiotherapy", "radiation therapy", "irradiation", "immunotherapy", "chemoradiotherapy", "chemoradiation", and "hyperthermia". These terms were then combined with the search terms for the following study designs or publication types: practice guidelines, meta-analyses, and randomized controlled trials (Appendix 2 in the original guideline document). In addition, the National Cancer Institute (NCI) (formerly the Physician Data Query [PDQ] database on the Internet [http://www.cancer.gov/search/clinical_trials/]) and the conference proceedings of the 1997 to 2007 annual meetings of the American Society of Clinical Oncology (ASCO) and the 1999 to 2006 annual meetings of the American Society for Therapeutic Radiology and Oncology (ASTRO) were searched for reports of new or ongoing trials. Relevant articles and abstracts were reviewed, and the reference lists from these sources were searched for additional trials. This formal search was supplemented with published abstracts from thoracic surgery and oncology conferences, conversations with colleagues and experts in the field, and a review of textbooks related to esophageal oncology.

Inclusion and Exclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports, published abstracts, or meta-analyses of randomized trials of preoperative or postoperative treatments compared with surgery alone or surgery plus another preoperative or postoperative treatment in patients with resectable and operable thoracic esophageal cancer. Data on survival had to be reported. Other outcomes of interest were adverse effects and quality of life.

Exclusion Criteria

Carcinomas located in the cervical esophagus were excluded.

NUMBER OF SOURCE DOCUMENTS

Thirty-nine randomized trials, and ten meta-analyses, including two Cochrane reviews were identified.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Because diverse treatment strategies were evaluated, the eligible studies were grouped into 13 basic treatment approaches (Table 1 in the original guideline document). An individual patient data (IPD)-based meta-analysis is believed to be the highest level of evidence available and was used if available in the published literature. If no IPD meta-analysis was available, a literature meta-analysis using estimated time-to-event hazard ratios was considered as the next-highest level of evidence. If neither of these methods were available in the literature, data were pooled by the Gastrointestinal Disease Site Group (GI DSG) at a common time-point (e.g., mortality at one or three years). The time point selected for meta-analyses must be clinically credible and relevant but not so far along the survival curve that wide confidence intervals result from fewer patients contributing to the estimate. Since time points prior to the median will generally ensure that there is sufficient data to be credible, the median survival times, weighted by the size of the treatment arms, were calculated to determine an appropriate time point for each meta-analysis.

Pooling was conducted using one-year mortality data for all meta-analyses except for the comparison of postoperative chemotherapy versus surgery alone, for which three-year mortality data was considered most appropriate for pooling. Studies that did not provide values for survival at the time of pooling were not included in each meta-analysis, although they were included in calculating the weighted median survival time, if values were provided. A meta-analysis software package, Review Manager 4.2 (Metaview© Update Software), available through the Cochrane Collaboration, was used. Pooled results were expressed as mortality risk ratio (RR) with 95% confidence interval (CI) using the random effects model. A RR less than 1.0 favours the treatment arm and an RR greater than 1.0 favours the control arm. The denominator in the pooled analysis is the number of randomized patients unless results for only the evaluable or eligible patients were reported. Heterogeneity of study results was assessed using a visual plot of the outcomes and by calculating the Chi-square statistic using a planned cut-off for significance of $p<0.05$.

Study Quality Evaluation

For comparisons for which new evidence was available since the publication of the original guideline in 2004, each trial was assessed for important study quality characteristics, including reporting of funding, randomization method, blinding, statistical power, follow-up, and intention-to-treat analysis.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Development and Internal Review

This evidence-based series (EBS) was developed by the Gastrointestinal Disease Site Group (GI DSG) of the Cancer Care Ontario (CCO) Program in Evidence-based Care (PEBC). The series is a convenient and up-to-date source of the best available evidence on preoperative or postoperative therapy for resectable esophageal cancer, developed through review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario. The GI DSG comprises medical oncologists, radiation oncologists, surgeons, a methodologist, and a community representative. For a complete list of the GI DSG members, please visit the CCO Web site at http://www.cancercare.on.ca/.

This evidence-based series replaces the original version of this report first completed in 2002 and published in 2004. The original guideline recommended surgery alone as the standard practice for resectable esophageal cancer. Since the publication of the guideline, several meta-analyses of randomized controlled trials (RCTs) have become available and the DSG agreed that the results of the highest quality meta-analyses support a recommendation for preoperative therapy. After much discussion, the DSG reached a general consensus that preoperative chemoradiotherapy should be the preferred modality, with preoperative chemotherapy alone as an alternative approach.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Report Approval Panel

Prior to the submission of this evidence-based series (EBS) draft report for external review, the report was reviewed and approved by the Program in Evidence-based Care (PEBC) Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues.

External Review by Ontario Clinicians

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base (in the original guideline document) of this EBS and the review and approval of the report by the PEBC Report Approval Panel, the Gastrointestinal Cancer Disease Site Group (GI DSG) circulated Sections 1 and 2 to external review participants in Ontario for review and feedback.

Methods

Feedback was obtained through a mailed survey of 133 external review participants in Ontario (29 medical oncologists, 19 radiation oncologists, 37 general surgeons, 29 thoracic surgeons, and 19 gastroenterologists). The survey consisted of items evaluating the methods, results, and interpretative summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Gastrointestinal Cancer Disease Site Group (GI DSG) reviewed the results of the survey.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Preoperative cisplatin-based chemotherapy plus radiotherapy is recommended as the preferred modality for the management of surgically resectable patients with esophageal cancer.
- Preoperative cisplatin-based chemotherapy alone is an alternative choice for the management of surgically resectable patients with esophageal cancer.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by meta-analyses and randomized trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- A literature meta-analysis of 10 randomized trials comparing preoperative chemoradiotherapy followed by surgery to surgery alone showed a 13% absolute benefit in survival at two years for preoperative chemoradiotherapy (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.70-0.93; p=0.002).
- A published abstract of an individual patient data (IPD)-based meta-analysis of nine randomized trials (2,102 patients) comparing preoperative chemotherapy followed by surgery (CT+S) to surgery alone demonstrated a 4% (from 16 to 20%) absolute overall survival advantage for chemotherapy at five years (HR, 0.87; 95% CI, 0.79-0.95; p=0.003). Based on seven trials (1,849 patients), the HR for disease-free survival (DFS) was 0.82 (95% CI, 0.74-0.91; p=0.001) in favour of chemotherapy plus surgery, representing a five-year absolute DFS benefit of 4% (from 6 to 10%). No difference was seen in postoperative death (6.7%).
- Randomized trials demonstrated no survival benefit for radiotherapy given alone, either preoperatively or postoperatively, compared with surgery alone.
- Randomized trials demonstrated no survival benefit for postoperative chemotherapy given alone compared with surgery alone.

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The Gastrointestinal Cancer Disease Site Group (GI DSG) acknowledges there is evidence indicating survival benefits with either preoperative chemotherapy or chemoradiotherapy compared with surgery alone. No direct comparison between preoperative chemoradiotherapy versus preoperative chemotherapy alone is available. Based on the majority of the evidence available at this time, the GI DSG believes that preoperative chemoradiotherapy for resectable carcinoma of the esophagus is the preferred approach.
- Clinicians should recognize that the survival advantage of preoperative therapy may be minimal and a discussion with patients regarding potential adverse effects is required. Decisions to administer preoperative therapy should be based on patient preferences, comorbidities, and suitability for trimodality therapy.
- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2002 Apr (revised 2008 May 21)

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Gastrointestinal Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Gastrointestinal Cancer Disease Site Group (GI DSG) were polled for potential conflicts of interest. No conflicts were declared.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on May 14, 2004. The information was verified by the guideline developer on June 2, 2004. This summary was updated by ECRI on September 9, 2005. The updated information was verified by the guideline developer on October 3, 2005. This NGC summary was updated by ECRI Institute on December 17, 2008.

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Date Modified: 2/23/2009